

Multi-Center Study Protocol 102.1

A randomized controlled study comparing Synergo® System adjuvant hyperthermia treatment in conjunction with Mitomycin C (LHT + MMC) versus BCG immunotherapy (BCG) adjuvant treatment in patients with Superficial Transitional Cell Carcinoma of the Bladder (STCCB)

Study Sponsor:

Medical Enterprises Europe B.V. (MEE)

Assumburg 152 b, 1081 GC, Amsterdam, The Netherlands

Tel +31-(0)20-642 3719, Fax +31-(0)20-642 1161

Email: synergo-med@planet.nl

www.medical-enterprises.com

Contact in Israel:

MEL- Medical Enterprises Ltd.

Tel +972-(0)3-9244830, Fax +972-(0)3-9245340

Chief Investigator:

J.A. Witjes, M.D., Ph.D.,

Department of Urology, Radboud University Hospital,

Nijmegen, The Netherlands

Tel +31 24 3613920 Fax +31 24 3541031

Protocol 102.1 Ver 2.0

Includes Protocol 102.1 Ver 1.0 dated 31 Oct 2001

And amendments 1-4 to the protocol.

© Copyright MEL Ltd. 2003

Table of contents

1	Introduction.....	3
2	Device description.....	4
3	Objectives of the study.....	4
4	Study population and patient selection	4
4.1	Study population	4
4.2	Participating centers	4
4.3	Patient selection	5
5	Study design.....	6
6	Treatment procedure	9
6.1	Induction phase	9
6.2	Maintenance phase (following induction phase)	9
6.3	Toxicity and dose / schedule modification	9
7	Patient examination and evaluation methods.....	12
7.1	Pre-study evaluation.....	12
7.2	Follow up visits.....	12
8	Response criteria	12
9	Risks and Benefits.....	13
9.1	Risks.....	13
9.2	Benefits	13
10	Patient discontinuation and replacement.....	13
10.1	Patient discontinuation.....	13
10.2	Replacement of patients	13
10.3	Protocol deviations.....	13
11	Statistical considerations.....	14
11.1	Null hypothesis	14
11.2	Alternative hypothesis.....	14
11.3	Sample size	14
11.4	Randomization	14
11.5	Statistical analysis	14
11.6	Interim analysis	15
12	Investigator authorization procedure	15
13	Study administration procedures.....	15
13.1	Study administration	15
13.2	Study monitoring.....	16
13.3	Ethical considerations	16
13.4	Data collection	16
13.5	Data management.....	16
13.6	Adverse event reporting	16
14	References.....	19
15	Appendices.....	20
	Appendix I: Definition of CIS and CIS sub-group in Protocol 102.1.....	20
	CIS sub-group in 102.1 Protocol.....	20
	Appendix II: Study Terms Definitions	21
	Appendix III: TNM Clinical Classification	22
	Appendix IV: Cystoscopy Landmarks	25
	Appendix V: W.H.O. Performance Status Scale	26
	Appendix VI: COMMON TOXICITY CRITERIA (CTC)	27
	Appendix VII: Participating centers	28

1 Introduction

The expected incidence of Transitional Cell Carcinoma of the Bladder (TCCB) in the United States is more than 50,000 new cases per year, with 70-80% of these cases being superficial (stage Ta, T1 and Carcinoma in situ (CIS)) (1). The disease is known to recur after surgical eradication and the risk to develop an aggressive infiltrating lesion varies among patients depending on their risk factors. The European Association of Urology has defined STCCB risk factor groups as follows:

Low risk: single tumors, Ta, G1, \leq 3cm

Intermediate risk: Ta-T1, G1-2, multifocal, $>$ 3cm

High risk: T1, G3, multifocal or highly recurrent, CIS

Standard treatment for intermediate-high risk superficial TCCB patients consists of complete transurethral resection (TUR) of all visible lesions, followed by intravesical chemotherapy or immunotherapy as prophylactic treatment. It is well known that prophylactic treatment results in a better outcome than TUR alone (2-5). The literature reports recurrence rates of up to 80% in intermediate-high risk superficial TCCB patients receiving TUR alone, with up to 20 years of follow-up (6,7). Recurrence rates following TUR and intravesical chemoprophylaxis seem to decrease to 25-50% in 2 years of follow-up (5,6,8) with minimal side effects. However, despite the prolongation of the disease free interval, adjuvant chemotherapy has no apparent long term impact with respect to time to progression or survival (9). Progression rates are usually not reduced, and are approximately 10-20% in 5 years follow-up (1,10,11).

A more recent treatment modality uses immunoprophylaxis (induction & maintenance) with live attenuated *Bacillus Calmette-Guérin* (BCG) instilled intravesically. The observed reduction in tumor recurrence rates ranges from 20% to 65% (average benefit of 40%) with BCG which is considered superior to chemotherapy (1,12).

BCG treatment has also not shown a reduction in progression rates, as with chemoprophylaxis (1,12-16). However, immunotherapy is known to be costly and to induce occasionally hazardous side effects, such as cystitis, symptoms of tuberculosis and even full blown sepsis, interfering with scheduled treatments (5).

Patients with carcinoma in situ are at highest risk of progression and about 50% of these patients treated with TUR alone will develop invasive disease and eventually die within 21 months (12,17). Chemo-ablation therapy generally offers 20-50% complete response for CIS whereas BCG offers 65-72% complete response for these patients (17-19).

It can be concluded that both intravesical chemotherapy and BCG immunoprophylaxis reduce recurrence, but not progression. BCG ablation therapy offers CIS patients better results than other regimens. However, patients treated with BCG are subjected to significant side effects, exposing them to substantial risks. The risk-benefit ratio of BCG treatment encourages the development of another treatment modality.

In the last two decades many experimental studies have shown that local hyperthermia combined with selected chemotherapeutic agents provides additive or synergistic antitumoral effect on solid tumors, including superficial transitional cell carcinoma of the bladder (9,10,20). Since 1988 the SB-TS 101 Synergo® System, a specifically designed technology to deliver simultaneous local bladder hyperthermia and intravesical chemotherapy, has been clinically tested. The clinical feasibility, safety and effectiveness of this approach for superficial bladder tumors have been proven to significantly reduce recurrence rates with minimal side effects (21). In a yet unpublished randomized study, intermediate-high risk superficial TCCB patients treated with this System, had recurrence rates of 25% compared to 65% in the control group treated with MMC instillations, in a 5 year follow-up.

The following protocol has been established in order to evaluate and compare the efficacy and safety of Synergo local hyperthermia in conjunction with intravesical chemotherapy (MMC) versus intravesical instillation of BCG for prophylaxis of recurrence in intermediate-high risk patients suffering from superficial TCCB.

2 Device description

The Synergo® System, is a computer-embedded intravesical irrigation system combined with an energy-delivering unit. The irrigation system consists of a disposable tubing line and catheter system. The energy-delivering unit consists of a radio frequency (RF) generator and an antenna. The treatment employs intravesical instillations of a chemotherapeutic agent concomitant with hyperthermia of the bladder walls induced by emission of RF energy, monitored by internal thermocouples. A specially designed combination of hardware and real-time software regulate the operation presenting the processed data on the monitor screen. The object of treatment is to heat the bladder walls while instilling the drug solution. The drug solution is cooled by the heat exchanger and continuously circulated in a closed circuit. The System consists of a computer, monitor with touch screen and keyboard as user's interfaces. It further includes an RF generator that delivers radio-frequency energy at 915 MHz, a drug circulating unit and a microprocessor with application specific software. Application specific software monitors and records treatment parameters during an actual session and provides a user interface that instantly alerts the operator regarding "out-of-range" parameters. The catheter itself is a sterile triple lumen, silicone, transurethral Foley type catheter. It provides the drug intravesical instillation. It is loaded with thermocouples for bladder walls temperature monitoring, and an RF antenna, which radiates the bladder walls, causing them to be heated to the desired temperature. There are two more thermocouples on the feeding cable, which are used for male patients to verify the temperatures in the area of the prostatic urethra. A balloon provides the anchoring of the catheter to the bladder neck. The tubing line, connected at one end to the drug circulating unit and at the other end to the catheter system, is used for circulating the drug solution to and from the bladder.

3 Objectives of the study

Comparison of Synergo delivered local hyperthermia (LHT) combined with intravesical instillation of Mitomycin C (MMC) versus intravesical instillation of immunotherapy Bacillus Calmette Guérin (BCG) for adjuvant (prophylactic) treatment, in patients with intermediate-high risk superficial transitional cell carcinoma of the bladder (STCCB).

3.1 The study is designed to evaluate the efficacy of the Synergo device by comparing

- * recurrence free survival; or
- time to complete response in CIS (Appendix I) and;
- * progression rate (to disease stage>T1) and/or metastatic disease

3.2 The study is designed to evaluate the safety of the Synergo device with regard to

- * local and systemic side effects, both subjective and objective

4 Study population and patient selection

4.1 Study population

Patients with intermediate-high risk superficial transitional cell carcinoma of the bladder undergoing transurethral resection of their tumors as part of the routine medical treatment.

4.2 Participating centers

See Appendix VII

4.3 Patient selection

4.3.1 Inclusion criteria:

- 4.3.1.1 Pathological findings of last TUR (Appendix II) of bladder:
Superficial TCC: Any G3 or any T1 and/or CIS* (Appendix I, III); or
Multifocal (>1) Ta lesions and/or multiple recurrences (>2) of Ta lesions in the last 24 months.
- 4.3.1.2 Complete tumor eradication must be confirmed by:
urine cytology (Appendix II); and
video-cystoscopy (Appendix II, IV) with pathological examination of biopsies from: any suspected areas, in cases with pre-treatment diagnosis of T1G3 or any tumor with concomitant CIS*, in cases with positive urine cytology;
Pure CIS* patients (with no exophytic tumor) will **not** require biopsies following TUR prior to study entry.
only CIS* lesions may remain tumor positive in biopsy or urine cytology examinations
- 4.3.1.3 WHO performance status 0-2 (Appendix V).
- 4.3.1.4 Life expectancy of more than 24 months.
- 4.3.1.5 Patients willing to sign informed consent according to ICH/EU GCP, and national/local regulations.

* Note: This study protocol includes positive CIS patients. Refer to appendix I for specific issues related to these patients

4.3.2 Exclusion criteria:

- 4.3.2.1 Bladder tumors other than TCC
- 4.3.2.2 Coexistence of another primary malignant tumor other than BCC of the skin
- 4.3.2.3 TCC of the bladder involving the urethra or upper urinary tract
- 4.3.2.4 Previous history of TCC stage T2 or higher
- 4.3.2.5 Clinical presence or previous history of regional spreading or distant metastases
- 4.3.2.6 Intravesical MMC treatments during the last 12 months
- 4.3.2.7 Previous intravesical BCG therapy:
 - a. Any intravesical BCG therapy in the last 24 months prior to the present TURBT
 - b. More than 6 BCG intravesical instillations in the last 48 months prior to the present TURBT.
- 4.3.2.8 Previous pelvic radiotherapy or systemic chemotherapy
- 4.3.2.9 Partial cystectomy
- 4.3.2.10 Diverticle of bladder larger than 1cm in diameter
- 4.3.2.11 Residual urine > 100cc measured by uroflowmetry
- 4.3.2.12 Bladder volume < 150cc measured by ultrasound
- 4.3.2.13 Urinary incontinence (more than one wet pad a day)
- 4.3.2.14 Urethral stricture impeding 20F catheterization
- 4.3.2.15 Urethral bleeding or persistent hematuria
- 4.3.2.16 Active intractable or uncontrollable UTI
- 4.3.2.17 Active tuberculosis or BCG infection
- 4.3.2.18 Patients who experienced BCG life threatening sepsis
- 4.3.2.19 Known allergy to MMC or BCG
- 4.3.2.20 Known impaired immune response, positive HIV serology, patients receiving systemic steroids or immunosuppressive therapy

- 4.3.2.21 Hematological disorders; leukocytes < 3500, platelets < 100,000
- 4.3.2.22 Kidney or liver function disorders (more than 1.5 times upper normal limit)
- 4.3.2.23 Pregnant or lactating women
- 4.3.2.24 Patients who cannot be followed up properly or are unable to collaborate

4.3.3 Informed consent

All patients will be asked to give their permission to take part in the study after the investigator has given them a full description of its purpose. Written informed consent will be obtained from the patient prior to performing any study- related procedure.

5 Study design

- 5.1 The study is designed to be a prospective, randomized, multi-centric, controlled clinical study. Its aim is to compare the treatment group to a control group with regard to the described objectives of the study.
- 5.2 The treatment group will include LHT+MMC (Kyowa) delivered by the Synergo® System, administered in 6 weekly induction sessions and 6 maintenance sessions. The control group will include one vial of OncoTICE® BCG (5x10⁸ bacilli) or One vial of Pasteur D (1x10⁹ bacilli) or One vial of RIVM (5x10⁸ bacilli) or One vial of Connaught (1x10⁹ bacilli) administered in 6 weekly induction sessions and 3 weekly repeated maintenance sessions (3x3). When choosing a BCG strain, the same strain must be used through the entire treatment course. If any strain used **other than OncoTice**, the investigator should specify the strain used in Form E of the CRF in the “drug lot number” paragraph for each treatment. Both groups include induction and maintenance treatment phases administered over a period of one year. See Table 1 – Treatment schedule.
- 5.3 Last TUR will be performed within 3-6 weeks prior to first study treatment session. In case a second TUR (video recorded) is conducted for verification of complete tumor eradication, the treatment session should begin 3-8 weeks after the initial TUR. Pathological stage and grade of the tumor will be evaluated in the last positive TUR, according to Appendix III.
- 5.4 Tumor free patient eligibility will be evaluated according to the inclusion and exclusion criteria. If patient’s eligibility enables him/her to be enrolled in the study, the physician will obtain the signed informed consent form.
- 5.5 Complete tumor eradication will be confirmed 14-28 days prior to the first study treatment session by visual video-cystoscopy examination and urine cytology;
 - Video-cystoscopy will be performed and biopsies taken from suspected areas and in cases with pre-treatment diagnosis of T1G3 or any tumor with concomitant CIS.
 - Urine cytology examination is mandatory. If urine cytology is positive, tumor origin will be sought by mapping the urinary tract.
 - Positive biopsies or urine cytology examinations demonstrating CIS lesions may be included in the study.
- 5.6 Bladder volume and residual volume will be measured by uroflowmetry and ultrasound respectively at pre-study evaluation.
- 5.7 Following patient enrollment, the Randomization, the Demographic and the Eligibility forms with current and historical clinical information will be completed by the investigator and sent to the sponsor.
- 5.8 Patients will be randomly assigned to either one of the study groups by the sponsor and treated according to section 6. Treatment forms will be completed recording each treatment session.
- 5.9 Patients will be instructed to refrain from diuretic beverages and reduce fluid intake 12 hours before each treatment session.
- 5.10 Patients will be followed-up for 24 months.

5.11 Follow-up will be performed every 3 months and consists of:

Urine cytology

Control video-cystoscopy with biopsies from any suspected areas and in cases of positive urine cytology. Mandatory biopsies will be taken in patients with pre-treatment diagnosis of T1G3 or any tumor with concomitant CIS on the first follow-up video cystoscopy (i.e., 7 weeks following the last induction treatment). If for any reason biopsies are taken, sessions will be postponed until negative results are confirmed.

Pure CIS patients (with no exophytic tumor) will **not** require biopsies on the first follow-up video cystoscopy (i.e., 7 weeks following the last induction treatment)

Further evaluation as outlined in section 7.2.3

5.12 The above clinical information will be recorded on appropriate Follow-up Visit forms, including all examinations results.

5.13 Patients will terminate treatment in the study and control groups following:

Tumor recurrence according to section 5.14

Disease progression (muscle invasion) or metastases

Adverse event preventing treatment or postponing it for longer than 2 weeks

All patients will be followed-up for at least 24 months regardless of tumor recurrence, progression, metastases, etc. Patients no longer receiving treatments will present for the study's follow-up visits, and will receive therapy according to the physician's decision.

Patients will terminate study participation completely following:

Study completion at 24 months

Withdrawal of informed consent

When a patient terminates study participation, the investigator will complete the Study termination form.

Patients who have successfully completed at least 6 BCG induction treatment sessions in the control group or at least 6 Synergo+MMC induction treatment sessions will be included in the "per protocol patient cohort".

5.14 Patients with a tumor recurrence during the 12 months of treatment will undergo tumor resection followed by resumption of treatment. Patients with a tumor recurrence after 12 months of treatment or a second tumor recurrence within 12 months of treatment or a tumor recurrence involving a T1G3 tumor will terminate the study treatments, although they will continue to present for the study follow-up visits. In the event that a tumor eradication procedure is performed, the next treatment session will be conducted 4 weeks following the procedure. The physician will indicate in the CRF the precise location of the tumor recurrence in the urinary bladder.

5.15 CRFs will be completed by the investigator at enrollment, at each treatment session, at follow-up visits and in the event of patient complaint or physician's observations of adverse events. Patient subjective complaints as well as physician's objective observations will be recorded at each treatment or follow-up visit.

5.16 CRFs will include data regarding number of missed working days due to treatment effects (not including session day), for working patients, in order to evaluate the financial benefits of one treatment over the other.

5.17 Long term follow-up (more than 2 years) will be initiated at selected clinical sites (to be determined at a later date).

Table 1 - Treatment schedule

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
LHT+MMC	+	+	+	+	+	+							UC	+
BCG	+	+	+	+	+	+							UC	+

Week	15	16	17	18	19	20	21	22	23	24	25	26	27	28
LHT+MMC							+					UC		+
BCG	+	+										UC	+	+

Week	29	30	31	32	33	34	35	36	37	38	39	40	41	42
LHT+MMC								+				UC		
BCG	+											UC		

Week	43	44	45	46	47	48	49	50	51	52	53	54
LHT+MMC		+							UC	+		
BCG									UC	+	+	+

Legend: + Treatment session
 U Urine cytology
 C Cystoscopy

6 Treatment procedure

Upon completion of pre-treatment evaluation and no later than 6 weeks after last TUR and 28 days after negative video-cystoscopy, all patients will be treated as follows:

6.1 Induction phase

Six weekly sessions of:

- 6.1.1 Treatment Group: 40mg of Mitomycin C (Kyowa) dissolved in 100mL sterile distilled water (delivered in 2 portions of 20mg in 50mL in two half hour periods), combined with local hyperthermia at $42\pm 2^{\circ}\text{C}$ induced by the Synergo® System.
- 6.1.2 Control Group: One vial of OncoTICE® BCG (5×10^8 bacilli) or One vial of Pasteur D (1×10^9 bacilli) or One vial of RIVM (5×10^8 bacilli) or One vial of Connaught (1×10^9 bacilli) dissolved in 50mL of NaCl 0.9% instilled in the bladder and sustained for 120 minutes.

6.2 Maintenance phase (following induction phase)

- 6.2.1 Treatment Group: One treatment session administered every 6-8 weeks, (total of 6 maintenance sessions), over a period of 12 months (refer to Table 1 – Treatment schedule).
- 6.2.2 Control Group: Three successive weekly treatment sessions administered once every 2-4 months, (total of 9 maintenance sessions), over a period of 12 months (refer to Table 1 – Treatment schedule).

6.3 Toxicity and dose / schedule modification

In this protocol the toxicity will be measured using the Common Toxicity Criteria (CTC) (Appendix VI, ref. 23). In grading the toxicity, the worst grade observed will be reported.

- 6.3.1 Toxicity of Mitomycin C administered intravesically is well known. Less than 10% of chemical or bacterial cystitis can be expected leading to some delay in the instillation schedule (22). Systemic toxicity such as allergic reactions, skin rash, etc. may occur and physician will decide on symptomatic treatment and consider whether to delay or discontinue further treatment. In cases of cystitis, treatment consists of antibiotics and anti-spasmodic medications.
- 6.3.2 BCG toxicity may be more severe with higher rates of local side effects. Systemic toxicity consists of fever, allergic reactions, malaise, etc. Tubercular disease may occur either locally (granulomatous change of bladder wall, prostatitis, epididymitis) or in the form of generalized disease. In the case of severe side effects Isoniazid therapy will be started at once and instillation therapy discontinued.
- 6.3.3 Mitomycin C can cause minor irritative bladder symptoms, which can be relieved using symptomatic medication, such as Phenazopyridine or Oxybutinin. BCG can cause more intense urinary frequency, urgency and pain in the bladder region. All these symptoms subside spontaneously or after medication within 48 hours. A slight elevation of body temperature ($<38^{\circ}\text{C}$) and infrequently a flu-like syndrome of short duration may occur after BCG. Paracetamol will be administered and it is effective in most cases. About 5% of cases experience more prominent local or systemic side effects, which require appropriate treatment (see Table 2 – Therapy recommendation for side-effects due to treatment).
- 6.3.4 *In vitro* studies have demonstrated that some anti-bacterial drugs can eradicate BCG. Among these are Trimetoprim-sulphamethoxazole and Quinolones, which will be avoided in treating bacterial cystitis.
- 6.3.5 In case of administration of Isoniazid for treating BCG side effects (Table 2), alcohol consumption must be avoided because it can increase serum transaminase levels and symptoms of Isoniazid-induced hepatitis.
- 6.3.6 No dosage modification of either drug is allowed. Instillations may be delayed in the case of side effects according to the recommendations listed in Table 2.

- 6.3.7 In case of toxicity resulting in treatment delay for more than 2 (two) weeks or requiring permanent discontinuation of either drug according to Table 2, the patient will terminate study treatments and will be further treated at physician's discretion.
- 6.3.8 In case of hyperthermia induced side effects, such as severe bladder spasms that may cause spillage of the MMC from the bladder, anti-cholinergic drugs may be given as listed in Table 2.
- 6.3.9 In case of severe pain due to the heating effects of the Synergo® System, increased pump flow and/or reduction of RF power to a endurable level (see Table 2), should be induced.
- 6.3.10 In case of persistent side effects, mentioned in sections 6.3.8-6.3.9 during more than two consecutive sessions, the patient will terminate the study treatments and continue only follow-up visits.

Table 2 – Therapy recommendations for side-effects due to treatment

Side effects (refer to NCI-CTC version 2.0) – Reference 23	Suggested intervention	LHT+MMC or BCG
Fever grade 1	Treat at physician's discretion	Delay treatment at physicians discretion
Fever grade > 1	Symptomatic therapy or Isoniazid 300mg daily for 3 months if BCG related	Delay treatment until asymptomatic ¹
Presence of genito-urinary symptoms (bladder spasms, dysuria, hematuria urinary frequency, urinary retention) grade 1 or 2	Antispasmodic drugs and/or antibiotics following antibiogram (if applicable)	Delay treatment until asymptomatic ¹
Presence of genitourinary symptoms grade >2	Antispasmodic drugs and/or antibiotics	Permanently discontinue protocol treatment
Presence of dysuria spasms and pain related to hyperthermia	Anti-cholinergic drugs P.O. or Intravesically before next treatment Increase pump flow or reduce RF energy	Delay treatment at physician discretion Delay treatment if bladder temperature < 40°C ¹
Allergic reaction or hypersensitivity grade 1-2 due to either BCG or MMC	Anti-histaminic drugs Consider prednisone	Consider treatment delay or discontinuation due to allergic reaction Delay treatment MMC ¹
Allergic reaction or hypersensitivity BCG/MMC related grade >2	Full 3 anti TB drug therapy for 3-6 months (for BCG patients)	Permanently discontinue protocol treatment
Severe illness related to BCG or BCG sepsis	Same as above twice daily and consider prednisone	Permanently discontinue protocol treatment
Urinary incontinence	Wait 1 week and diagnose with flexible cystoscopy	Delay treatment until problem resolves

¹ In case persisting toxicity results in treatment delay for more than 2 (two) consecutive weeks, patients will terminate study treatments and will be treated at the discretion of the physician and remain in the study for follow-up visits only.

7 Patient examination and evaluation methods

7.1 Pre-study evaluation

The following examinations will be performed prior to the first treatment session.

- 7.1.1 Negative tumor status will be confirmed by video-cystoscopy with pathological examination of any suspected area (in cases of pre-treatment diagnosed T1G3 or any tumor with concomitant CIS- random biopsies are mandatory); and urine cytology. Only CIS lesions may remain tumor positive in biopsy or urine cytology
- 7.1.2 Medical history (general and urological) and clinical assessment
- 7.1.3 Uroflowmetry and ultrasound for bladder volume and residual urine volume determination, respectively
- 7.1.4 Complete blood count and blood chemistry
- 7.1.5 Urinalysis and urine culture
- 7.1.6 Upper urinary tract imaging: Intravenous pyelography (IVP) or Computerized Tomography (CT) with contrast medium or Ultrasound (US) with visibility of the upper urinary tract should be conducted up to six months prior to the randomization date, to rule out metastases or other tumors in the upper urinary tract.
- 7.1.7 Pelvic computed tomography recommended to rule out metastases or other tumors
- 7.1.8 Signed informed consent

7.2 Follow up visits

Seven weeks after the last inductive treatment session, and every 3 months thereafter up to 24 months at least, the following examinations must be performed:

7.2.1 Urine cytology

7.2.2 Control video-cystoscopy, including biopsies:

from any suspected areas, and

in patients pre-treatment diagnosed T1G3 or any tumor with concomitant CIS on the first follow-up video cystoscopy (i.e., 7 weeks following the last induction treatment), and in cases of positive urine cytology

Pure CIS patients (with no exophytic tumor) will **not** require biopsies on the first follow up video cystoscopy (i.e., 7 weeks following the last induction treatment)

7.2.3 Further evaluation, including:

complete blood count, blood chemistry, urinalysis and urine culture at 12 and 24 month follow-ups, and

any additional examinations needed for evaluation

prior to the beginning of treatment or follow-up visits, physician's and/or patient's observations, complaints, etc. will be recorded on the appropriate form in the CRF (see adverse event reporting 13.6.)

bladder volume and residual urine measurement by uroflowmetry and ultrasound respectively at 12- month follow-up visit

pelvic CT is recommended at 12- month follow-up visit

8 Response criteria

Response to treatment will be assessed at each follow-up evaluation using the following nomenclature:

No Recurrence (NR): No evidence of recurrence of tumor/s in the bladder.

Recurrent Disease (RD): Biopsy confirmed TCC. Positive cytology will render seeking tumor origin by mapping the urinary tract.

Progressive Disease (PD): Occurrence of a muscle invasive tumor (>T1), and/or metastatic disease. Progression does not include occurrence of new T1 or CIS.

Complete Response (CR): No evidence of tumors in the bladder either in histopathological or in cytopathological examinations in the case of CIS lesions.

9 Risks and Benefits

9.1 Risks

The Synergo® System and principle of operation are such that the occurrence of adverse reactions is unlikely and hazard due to malfunction of the device is very low. Any adverse reactions reported by subjects or noted by study personnel will be recorded. Furthermore, the performance requirements of the device have been fully tested as set forth in the company's quality assurance system.

9.2 Benefits

Previous studies with the Synergo device treatments have proven to lower recurrence rates of superficial bladder TCC, which tend to re-appear despite surgical eradication.

10 Patient discontinuation and replacement

10.1 Patient discontinuation

Patients should be removed from the study whenever considered necessary for their welfare. Non-compliance with the protocol or the occurrence of a significant adverse event may necessitate discontinuing a patient. If a patient is discontinued, the reason must be entered on the Case Report Form and signed by the principal investigator. In the case of any questionable situation, the study monitor or Sponsor personnel should be consulted. Every attempt should be made to perform the follow-up examinations. Adverse events must be followed to resolution.

10.2 Replacement of patients

Patients will be replaced if they discontinue due to noncompliance or if they are lost to follow up.

10.3 Protocol deviations

When circumstances arise which suggest that a deviation from this protocol should be considered, the investigator or other physician in attendance must contact the study monitor by telephone as soon as possible prior to implementation. Any deviation from the protocol agreed to will pertain only to the individual patient/subject involved. The Case Report Form will describe the circumstances and identify the pertinent protocol procedure.

In the event that a protocol change is proposed for all patients, then the procedure for a protocol amendment should be followed. In either case, any modification of the protocol that may become necessary during the course of this study, other than to protect subjects from an immediate hazard, is subject to prior discussion between the clinical investigator and the study monitor.

11 Statistical considerations

11.1 Null hypothesis

The study is designed to compare the probability of recurrence of STCCB after two years in patients receiving the combined treatment (LHT+MMC) versus those receiving BCG therapy, therefore the null hypotheses will be that they are equal.

11.2 Alternative hypothesis

Patients receiving the combined treatment (LHT+MMC) have a lower probability of recurrence after two years.

11.3 Sample size

The above null hypothesis should be tested using the Mantel-Haenzel (log-rank) Test, the number of patients for this comparison will be calculated using the formula:

$$N = \frac{2d}{2 - P_{MMC+HT}(t) - P_{BCG}(t)}$$

$$\text{where } d = \left(z_{1-\alpha} + 2z_{1-\beta} \left(\frac{\theta^{1/2}}{1+\theta} \right) \right)^2 \left(\frac{1+\theta}{1-\theta} \right)^2, \text{ and } \theta = \frac{\log(P_{MMC+HT}(t))}{\log(P_{BCG}(t))}.$$

In previous studies for the combined treatment the two-year recurrence rate is about 25%, and the recurrence rate from the literature for BCG is 40%. Thus if we set $P_{MMC+HT}(t) = 0.75$ and $P_{BCG}(t) = 0.6$ ($t = 2$ years) then at a significance level of 0.05 and with a power of 80% a total of $N = 237$ are required.

Twenty percent drop-out is expected, therefore $N = 300$ patients should be recruited to the study, 150 in each study group.

11.4 Randomization

The patients will be randomized into the study, within centers, using a blocking method with the help of a random number generator.

11.5 Statistical analysis

11.5.1 General considerations

The required significance level of findings will be equal or lower than 5%. All statistical tests will be one-sided. Where confidence limits are appropriate, the confidence level will be 95%.

11.5.2 Data to be analyzed

Intent-to-treat and efficacy-subset analysis will be performed. The intent-to-treat analysis will include all data from patients enrolled in the study. Criteria for the efficacy-evaluable subset will be protocol compliance.

The descriptive statistical evaluation will include all available data from all patients using intent-to-treat analysis. The efficacy analysis will be performed using the efficacy-subset.

11.5.3 Efficacy analysis

The Null Hypothesis will be tested using the Log-rank Test. Time to event curves (disease free survival, time to first recurrence, time to complete response for CIS, time to progression or metastases) will be constructed using Kaplan-Meier estimates.

Baseline characteristics of the study population will be compared with the T-test or the Chi-squared test depending on the type of data.
We will justify as well pooling of the data.

11.5.4 Safety analysis

The analysis of adverse experiences will include incidence tables and incidence table by severity and relationship to treatment. This analysis is to be carried out over 12 months.

11.6 Interim analysis

One interim efficacy analysis will be performed at the end of one year using a significance level of 0.01. An independent study safety committee will be appointed by the sponsor for investigation of on-going safety of the study and interim analysis (at one year). The committee will include at least one scientist, a statistician and a physician not directly related to or participating in the clinical study. The committee will not report the study results to the investigators, although they may make safety recommendations to the study groups based on ethical considerations only.

12 Investigator authorization procedure

Investigators will be authorized to enroll patients to the trial at the site only after obtaining or fulfilling the following:

- a clinical trial agreement indicating that the investigator will fully comply with the protocol.
- the operating physician participating in the study will be trained by MEE B.V. and authorized to handle and use the Synergo® System after completion of a qualification course.
- the qualified investigator will conduct LHT+MMC treatments according to the Synergo® System User's Manual.
- the investigator and his staff will be trained by MEE B.V. or their CRO to conduct the study strictly according to the study protocol and all instructions provided to ensure uniform performance and recording procedures and according to GCP.
- A training verification form will be completed by MEE B.V. personnel for each staff member participating in the study, following the training session.
- a list of staff members authorized to sign Case Report Forms.
- a copy of the approval of the center's local or national ethics committee.
- one designated pathologist will be assigned in each center to examine all urological specimens from the center's study patients, according to the study protocol.

13 Study administration procedures

13.1 Study administration

Each investigational site will be trained at study implementation to conduct the study in accordance with the applicable procedures for conducting clinical investigations.

A study handbook shall be prepared for each site including all necessary paperwork required to be maintained at the site. Paperwork includes IRB/ethical committee approvals, study/investigator agreements, study protocol, and instructions for site personnel in how to qualify and enroll subjects and complete Case Report Forms.

A site coordinator shall be appointed at each site, to coordinate activities required at the site and liaison with the study monitor. The site coordinator shall manage patient recruitment, enrollment, randomization form completion and ensure that reporting to the Sponsor and CRFs are accurately completed and submitted in a timely manner to the data entry center.

13.2 Study monitoring

The sites shall be monitored to ensure that the investigators are conducting the clinical trials in compliance with the protocol, and applicable requirements and regulations. The study monitor will assess the quality of the clinical data and documentation being produced at the site, identify potential problem areas and recommend approaches to prevent problems from developing and solve existing problems.

13.3 Ethical considerations

Prior to study initiation each site shall obtain IRB/ethics committee approval of the clinical investigation. Any changes in the study protocol or changes in investigator must be re-approved by the IRB and the approval documented. All patients enrolled in the study must provide their written consent prior to entering the study. An informed consent form shall be signed and dated by the patient and retained by the investigator as part of the study records.

13.4 Data collection

The CRFs are completed at the site and an initial quality check is conducted by the site coordinator prior to forwarding the CRFs to the data entry center (The Sponsor).

13.4.1 Form attesting that this clinical study using Synergo hyperthermia and chemotherapy versus BCG immunotherapy has been approved by the Ethics Committee of each center

13.4.2 Signed informed consent for each patient

13.4.3 Randomization form used for patient randomization, Eligibility and Demographic forms to be sent to the sponsor with each patient recruited

13.4.4 CRFs to record demographic, treatment, follow-up visits, side effects and adverse events

13.4.5 Treatment termination form, Study termination form

13.4.6 Flow-chart per individual patient

13.5 Data management

A database management system will be designed and maintained, including screen preparation, data dictionary preparation and automated edit check programming. Pre-entry and post-entry quality control of the clinical data will be performed at the data entry center. Querying sites for missing, incorrect or illegible data shall be done by the data entry center.

13.6 Adverse event reporting

13.6.1 Definitions

An Adverse Event (AE) is any untoward medical occurrence, which does not necessarily have to have a causal relationship with the study procedure. This includes any physical or clinical change experienced by the subject, whether or not it is considered to be related to the study device. An AE can, therefore, be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease (including onset of new illness and exacerbation of pre-existing conditions) temporally associated with the use of the study device. All AE, must be recorded on the Case Report Form (refer to section 13.6.6 for Adverse event reporting method).

13.6.2 Classification of adverse events

Adverse events are classified as either **Serious** or **Non-Serious**:

13.6.2.1 **Serious Adverse Events (SAE)**

They are defined as any occurrence that suggests a significant hazard or side-effect of participating in a clinical study. SAE may or may not be related to the device.

An AE is considered serious if it:

- Requires intervention to prevent permanent impairment or damage
- Requires hospitalisation or prolongation of hospitalisation (hospitalisation for performing Transurethral Tumor Resection (TUR))

or taking bladder biopsies from any suspicious areas will not be considered a Serious Adverse Events)

- Is permanently disabling, i.e. incapacitating or interfering with the ability to resume normal life patterns
- Is a congenital anomaly or cancer
- Is fatal or life-threatening

13.6.2.2 **Non-serious Adverse Event**

Any other adverse event.

13.6.3 Adverse event causality

The following criteria (Karch, FE, Lasagna, L (1975), *Adverse Drug Reactions. A Critical Review. JAMA* 234 (12): 1236-4) are to be used for assessment of the causal relationship between the adverse event and the test device.

For classification, all criteria of one of the following categories must be met:

13.6.3.1 **Definite**

A reaction that follows a reasonable temporal sequence from exposure to device or procedure

Improvement or disappearance of symptoms on stopping or reducing the exposure time or intensity (de-challenge)

Reappearance of the reaction on repeated exposure (re-challenge)

13.6.3.2 **Probable**

A reaction that follows a reasonable temporal sequence from exposure to the study device or procedure

Confirmation of finding by de-challenge

The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other methods of therapy administered to the patient

13.6.3.3 **Possible**

Plausible temporal sequence

The adverse event might have been produced by the subject's clinical state (chronic illness, concomitant acute illness) or other modes of therapy administered to the patient

13.6.3.4 **Not Related**

Any reaction not meeting the above criteria

Current state-of-the-art medical technology indicates that a relationship is extremely unlikely. Re-challenge is negative

13.6.4 Adverse event severity

With respect to intensity, adverse events are classified as follows:

Mild	Awareness of sign, symptom or event, but easily tolerated
Moderate	Symptoms causing enough discomfort to interfere with usual activity and possibly to warrant intervention
Severe	Incapacitating event causing inability to perform usual activity or significantly affecting clinical status, warranting intervention
Life-threatening	Immediate risk of death

13.6.5 Action to be taken

In case of an Adverse Event, the clinical investigator will initiate appropriate treatment according to his medical judgment and will decide whether to withdraw the subject from the study. The adverse event will be recorded on the Adverse Event Reporting Form.

13.6.6 Adverse event reporting

Any serious adverse event (SAE):

Will be reported immediately to a representative of the sponsor by telephone within 24 hours of his/her becoming aware of the occurrence of a serious adverse event. The notification is to be followed by a written report within 10 days of such an event. The

investigator will also report any serious adverse events to the local and National ethical committee/IRB within 48 hours.

Record these SAEs on the following forms:

- Adverse Event Forms (section G)
- Serious Adverse Event Form (section J)

Any adverse event (AE):

Prior to the beginning of each treatment or follow-up session, report the AEs that occurred after the beginning of the last session but before the beginning of the current session.

Record these AEs on the following forms:

- Treatment Session and Adverse Event Grading Form (section E)
- Adverse Event Form (section J)

Make a record of AEs that occur **during** a session in the patient's file (source document) after that session. Report these AEs in the forms listed above prior to the beginning of the next session along with AEs that occurred during the time between sessions. In both study arms, do **not** report AEs during an active treatment session. However, AEs that occur during the patient's final session should be reported immediately after that session.

14 References

1. Kamat AH, Lamm DL: Intravesical therapy for bladder cancer. *Urology* 2000;55:161-168.
2. Soloway MS: Managing superficial bladder cancer: An overview. *Urology* 1992;40:5-10.
3. Lamm DL, Blumenstein B, Sarosdy M, et al: Significant long term patients benefit with BCG maintenance therapy: A southwest oncology group study. *J Urol* 1997;157:831.
4. Lamm DL, Blumenstein BA, Crawford, et al: A randomized trial of intravesical doxorubicin and immunotherapy with BCG for transitional cell carcinoma of the bladder. *N Eng J Med* 1991;325:1205-1209.
5. Lamm DL, Blumenstein BA, Crissman JD, et al: Maintenance BCG immunotherapy for recurrent Ta, T1 and Tis transitional cell carcinoma of the bladder: A randomized SWOG group study. *J Urol* 2000;163:1124-1129.
6. Brake M, Leortzer H, Horsch R, et al: Long term results of intravesical BCG therapy for stage T1 superficial bladder cancer. *Urology* 2000;55(5):673-677.
7. Herr WH: Natural history of superficial bladder tumors: 10-20 years follow-up of treated patients. *World J Urol* 1997;15:84-88.
8. Rodrigez FM, Toniolo GC, Bayarri JS, et al: Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol* 2000;164:680-684.
9. Pawinski A, Sylvester R, Kurth KH, et al: A combined analysis of EORTC and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer. *J Urol* 1996;156:1934-1941.
10. Witjes JA, Mungan NA, Debruyne NJ: Management of superficial bladder cancer with intravesical chemotherapy: An update. *Urology* 2000;56:19-21.
11. Oosterlinck W, Kurth KH, Schroder F, et al: A prospective European organization for research and treatment of cancer genitourinary group randomized trial comparing transurethral resection followed by a single intravesical instillation of Epirubicin or water in single Ta, T1 papillary carcinoma of the bladder. *J Urol* 1993;149:749-752.
12. Kurth KH, Bouffieux C, Sylvester R, et al: Treatment of superficial bladder tumors: achievements and needs. *Eur Urol* 2000;37(suppl 3):1-9.
13. Witjes JA, Caris CTM, Numgan NA, et al: Results of a randomized phase II trial of sequential intravesical therapy with Mitomycin c and BCG versus Mitomycin c alone in patients with superficial bladder cancer. *J Urol* 1998;160:1668-1672.
14. Herr HW: Tumor progression and survival of patients with high grade, non invasive (TaG3) bladder tumor: 15 years outcome. *J Urol* 2000;163:60-62.
15. Kerge S, Giani G, Meyer T, et al: A randomized multicentric trial of adjuvant therapy in superficial transitional cell carcinoma: TUR only versus TUR and Mitomycin c versus TUR and BCG. *J Urol* 1996;156:962-966.
16. Van der Meijden AP, Brausi M, Zambon V, et al: Intravesical instillation of epirubicin, BCG and BCG plus isoniazid for intermediate and high risk T1 papillary carcinoma of the bladder: a EORTC genito-urinary group randomized phase III trial. *J Urol* 2001;166:476-481.
17. Skinner DG, Richie JP, Cooper PH, et al: The clinical significance of carcinoma in situ of the bladder and its association with overt carcinoma. *J Urol* 1974;112:68-71.
18. Lamm DL: Carcinoma in situ. *Urol Clin North Am* 1992;19:499-508.
19. Kim JC, Steinberg GD: The limits of BCG for carcinoma in situ of the bladder. *J Urol* 2001;165:745-756.

20. Oosterlink W: The management of superficial bladder cancer. *BJU International* 2001;87:135-140.
21. Colombo R, Brausi M, Da Pozzo LF, et al: Thermo-chemotherapy and electromotive drug administration of MMC in superficial bladder cancer eradication. *Eur Urol* 2000 Apr;24:1-6.
22. Brackman RB, Swanson DA, Johnson DE, et al: Role of intravesical Mitomycin C in management of superficial bladder tumor. *Urology* 1998;24:11-15.
23. <http://ctep.info.nih.gov/CTC3/default.htm>.

15 Appendices

Appendix I: Definition of CIS and CIS sub-group in Protocol 102.1

Pathological guideline by Prof. F. Algaba

Flat lesion (non papillary) characterized by the presence of cells with large, irregular, hyperchromatic nuclei, with high grade anaplasia (similar to grade 3 in transitional cell carcinoma), that may be either present in the entire thickness of the epithelium or only in part of it.

The phenotypic spectrum is:

- Nuclear enlargement.
- Increased nuclear/cytoplasmatic ratio.
- Eccentric position of nuclei with nuclear clustering.
- Nuclear pleomorphism.
- Coarsy granular, irregularly distributed chromatin.
- Loss of polarity.
- Decreased intercellular adhesion.
- Loss of cytoplasmic glycogen.

CIS sub-group in 102.1 Protocol

Introduction: Chemo-therapy instillation generally offers 20-50% complete response for patients diagnosed with carcinoma in situ (CIS) whereas BCG offers 65-72% complete response for these patients (17-19), therefore, BCG immuno-therapy offers CIS patients better results than other regimens.

CIS sub-group: Patients suffering from superficial transitional cell carcinoma of the bladder diagnosed with CIS are considered high-risk patients and will be included in the study, according to their eligibility. The study protocol applies to CIS positive patients with the following exceptions:

Objectives: The objective of efficacy in these patients will be achieving “Complete Response” (CR), with no evidence of tumors in the bladder as indicated by urine cytology and biopsies.

Patient selection – Inclusion criteria: Pre-treatment diagnosed CIS cases may remain tumor positive in urine cytology and/or video-cystoscopy (with biopsies) during study entry.

Study design: In any tumor with concomitant CIS- random biopsies are mandatory at the first cystoscopy examination. Pure CIS patients will not require biopsies at the pre-inclusion video-cystoscopy or at the first follow up video-cystoscopy examination.

Treatment procedure: Randomization and treatment schedule as designated in the protocol.

Statistical considerations: The statistical analyses performed on this sub-group of subjects will cohere with the above efficacy objective. The safety statistical analysis will be according to the protocol for the general study population.

Appendix II: Study Terms Definitions

Last TUR = last transurethral resection performed **before** enrollment of patient for study candidacy. Performed 3-8 weeks before the first study treatment session. Pathological biopsy specimen will contain muscle layer.

Video-cystoscopy = the video-cystoscopy performed **before** enrollment of patient for study candidacy demonstrating visually negative (pre-study) (Appendix IV). Performed 14-28 days before first study treatment session. Biopsies from suspected areas and from pre-treatment diagnosed cases of T1G3 and/or any tumor with concomitant CIS are mandatory in and will be pathologically examined (only CIS cases may remain positive for inclusion in study).

Control video-cystoscopy = cystoscopy performed every 3 months during 24 months of follow-up (in the first control video-cystoscopy, 7 weeks after the last induction session, mandatory biopsies should be taken from any cases of T1G3 and/or any tumor with concomitant CIS). Done according to appendix IV. If positive – consider disease recurrence (except CIS cases).

Urine cytology = urine sample for cytopathological detection of suspicious cells for TCC. Performed at least one month apart from last instillation. If positive – tumor must be sought (except for CIS findings in cases pre-treatment diagnosed with CIS). Only biopsy can confirm tumor recurrence.

Appendix III: TNM Clinical Classification

UICC Fifth Edition -1997 Urinary Bladder (ICDO-O C67)

Rules for Classification

The classification applies only to carcinomas. Papilloma is excluded. There should be histological or cytological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories: Physical examination, imaging, and endoscopy.

N categories: Physical examination and imaging.

M categories: Physical examination and imaging.

Regional Lymph Nodes

The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.

TNM Clinical Classification

T -Primary tumor

The suffix (m) may be added to the appropriate T category to indicate multiple tumors. The suffix (is) may be added to any T to indicate presence of associated carcinoma in situ.

TX	Primary tumor cannot be assessed
----	----------------------------------

TO	No evidence of primary tumor
----	------------------------------

Ta	Non-invasive papillary carcinoma
----	----------------------------------

Tis	Carcinoma in situ: "flat tumor"
-----	---------------------------------

T1	Tumor invades subepithelial connective tissue
----	---

T2	Tumor invades muscle
----	----------------------

T2a	Tumor invades superficial muscle (inner half)
-----	---

T2b	Tumor invades deep muscle (outer half)
-----	--

T3	Tumor invades perivesical tissue
----	----------------------------------

T3a	microscopically
-----	-----------------

T3b	macroscopically (extravesical mass)
-----	-------------------------------------

T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
----	---

T4a	Tumor invades prostate or uterus or vagina
-----	--

T4b	Tumor invades pelvic wall or abdominal wall
-----	---

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
----	---

NO	No regional lymph node metastasis
----	-----------------------------------

N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
----	--

N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
----	---

N3	Metastasis in a lymph node more than 5 cm in greatest dimension
----	---

M - Distant metastasis

MX	Distant metastasis cannot be assessed
----	---------------------------------------

MO	No distant metastasis
----	-----------------------

M1	Distant metastasis
----	--------------------

pTNM Pathological Classification

The pT, pN, and pM categories correspond to the T, N, and M categories.

G Histopathological Grading

GX	Grade of differentiation cannot be assessed
----	---

G1	Well differentiated
----	---------------------

G2	Moderately differentiated
----	---------------------------

G3-G4	Poorly differentiated / undifferentiated
-------	--

Stage Grouping

Stage Oa	Ta	N0	M0
----------	----	----	----

Stage Ois	Tis	N0	M0
-----------	-----	----	----

Stage I	T1	N0	M0
---------	----	----	----

Stage II	T2a	N0	M0
	T2b	N0	M0

Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0

Stage IV	T4b	N0	M0
	Any T	N 1,2,3	M0
	Any T	Any N	M1

Appendix IV: Cystoscopy Landmarks

Cystoscopies (pre-study or control) should be video-recorded during the procedure.
The cystoscopy should include clear visualization of the following anatomical landmarks:

- Urethra
- Bladder neck
- Anterior wall
- Both ostea
- Dome
- Lateral bladder walls
- Posterior wall

Appendix V: W.H.O. Performance Status Scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self- care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self- care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self- care; totally confined to bed or chair.

Appendix VI: COMMON TOXICITY CRITERIA (CTC)

CTC Version 2.0

Publish Date: April 30, 1999

COMMON TOXICITY CRITERIA (CTC)

Grade	0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever <38°C (<100.4°F)	urticaria, drug fever ≥38°C (≥100.4°F), and/or symptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN					
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g. decrease in performance status by 1 ECOG level or 20% Karnofsky or <i>Lansky</i>) or causing difficulty performing	severe (e.g. decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or <i>Lansky</i>) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix 111 for performance status scales					
Fever (in the absence of neutropenia, where neutropenia is defined as AGC<1.0 x 10 ⁹ /L	none	38.0 – 39.0°C (100.4 – 102.2°F)	39.1 – 40.0°C (102.3 – 104.0°F)	>40.0°C(>104.0°F) for <24 hrs	>40.0°C(>104.0°F) for >24 hrs
Also consider Allergic reaction/hypersensitivity Note: The temperature measurements listed above are oral or tympanic					
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	severe symptoms requiring narcotic	-
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite	-
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clot	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube or surgery
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-

Appendix VII: Participating centers

1. Radboud University Hospital (Department of Urology)
Nijmegen, The Netherlands
Telephone: 31 24 3613920 Fax: 31 24 3541031
e-mail: f.Witjes@uro.azn.nl
Chief Investigator: J.A. Witjes, M.D., Ph.D.
Co-Investigator: A.G.van der Heijden M.D.
2. Tenon Hospital (Department of Urology)
Paris, France
Telephone: 33 1 56 01 82 17 Fax: 33 1 56 01 73 06
e-mail: calin.ciofu@tnn.ap-hop-paris.fr
Chief Investigator: Pr Gattegno
Co-Investigator: Dr Calin Ciofu M.D.
3. St. Louis Hospital (Department of Urology)
Paris, France
Telephone: 33 1 42499621 Fax: 33 1 42499616
e-mail: f.dgc@chu-stlouis.fr
Chief Investigator: Pr. F. Desgrandchamps M.D.
Co-Investigator: Dr A. Degouvello – Ch. Cauderlier
4. San Raffaele Hospital (HSR) (Department of Urology)
Milan, Italy
Telephone: 39 022 6432422/2303 Fax: 39 022 6432969
e-mail: colombo.renzo@hsr.it
Chief Investigator: R. Colombo, M.D.
Co-Investigators: LF. Da Pozzo, M.D., A. Salonia, M.D., R. Naspro, M.D.
5. University Policlinic Hospital (Department of Urology)
Palermo, Italy
Telephone: 39 091 6552410 Fax: 39 091 6552434
e-mail: vserretta@libero.it
Chief Investigator: Prof. V. Serretta, M.D.
Co-Investigators: Pr. M. Pavone, M.D., G.B. Ingragiola, M.D.
6. Wolfson Hospital (Department of Urology)
Holon, Israel
Telephone: 972 3 5028653 Fax: 972 3 5028651
e-mail: sidi@wolfson.health.gov.il
Chief Investigator: Pr. Ami Sidi, M.D.
Co-Investigators: A. Tarnopolski, M.D., A. Tsivian, M.D.
7. Bnai-Zion Hospital (Department of Urology)
Haifa, Israel
Telephone: 972 4 8359542 Fax: 972 4 8359524
e-mail: o.native@b-zion.org.il
Chief Investigator: Pr O. Nativ, M.D.
Co-Investigators: G. Mayer, M.D., A. Kravchov, M.D., M. Vald.

8. Hadassah Hospital (Department of Urology)
Jerusalem, Israel
Telephone: 972 2 6776874 Fax: 972 2 6430929
e-mail: ong1000@netvision.net.il
Chief Investigator: O. Gofrit M.D.
Co-Investigator: Pr. D. Pode M.D.

9. Hospital Erasme, (Department of Urology)
Brussels, Belgium
Telephone: 32 2 5553614 Fax: 32 2 5553699
e-mail: azlotta@ulb.ac.be
Chief Investigator: A.R. Zlotta M.D.

10. Istituto Europeo del Oncologia (IEO), (Department of Urology)
Milan, Italy
Telephone: 39 02 57489746 Fax: 39 02 57489746
e-mail: fabrizio.verweije@ieo.it
Chief Investigator: Pr. O. de Cobelli M.D.
Co-Investigator: F. Verweije M.D.

11. Krankenhaus Harlaching, (Department of Urology)
Munich, Germany
Telephone: 49 89 6210 362799 Fax: 49 89 17998806
e-mail: urologie@khhm.de
Chief Investigator: Pr. O. Chaussy M.D.
Co-Investigator: F. Hasner M.D.